The article in this issue by Ellam et al\(^1\) raises many interesting questions about the composition of diets, and their study fits with data showing that dietary issues are a major factor in the current epidemics of obesity, diabetes, and cardiovascular disease (CVD).\(^2-4\) Most studies have focused on lipid abnormalities or total calories. For instance, it has long been known that apolipoprotein E\(^{−/−}\) mice develop accelerated atherosclerosis\(^5\) and that this is affected by both age and gender.\(^6\) The novelty of the current study is that the authors demonstrate that the level of dietary phosphate has a direct relationship with the severity of the atherosclerotic lesions. Levels of phosphate intake and serum phosphate have been shown to directly correlate with atherosclerosis in humans\(^7,8\) and in various animal models, but it has never been clear whether phosphate levels are an associated factor or play a causal role. The most significant contribution of this relatively small study is that a modest reduction of phosphate intake in a mouse model with a genetic defect in lipid metabolism is associated with a reduction in atherosclerotic lesions and oxidative stress.

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It has long been known that chronic kidney failure is associated with high levels of phosphate and calcium, accelerated atherosclerosis, calcification of various parts of the cardiovascular system, and increased morbidity and mortality from CVD.\(^9\) A large study of patients with chronic kidney disease showed that among measurements of mineral metabolism, only serum phosphate levels correlated with patient outcomes.\(^10\) With respect to the source(s) of serum phosphate, a recent study by Moe et al showed that the source of phosphate in the diet has a major effect on the phosphate levels.\(^11\) Namely, in a comparison between phosphate from vegetable and meat sources, phosphate levels were significantly higher following consumption of meals based on meat. Because coronary artery calcification predicts both morbidity and mortality (especially in diabetics)\(^12\) and renal function may decrease with aging in many people, the issue of phosphate balance will likely assume greater importance in the near future.

The metabolic syndrome, including obesity, hyperlipidemia, and insulin resistance, is also associated with an increased risk of atherosclerosis.\(^13\) The current study reveals a paradoxical decrease in atherosclerotic burden in mice on a low phosphate intake in the face of an increase in both insulin resistance and fat accumulation in the liver and lipid storage areas, risk factors for CVD. These data are consistent with a cross-sectional study of normal subjects showing that high phosphate levels are associated with CVD risk and that low phosphate levels are associated with several aspects of the metabolic syndrome.\(^14\) They are also consistent with the observation that a diet rich in dairy products is correlated with the metabolic syndrome in obese but not lean men and women.\(^15\) The reasons why phosphate influences insulin/glucose metabolism are not clear, but such influences have been reported in the metabolic syndrome, obesity, and hypertension.\(^16,17\) The data from the current study, in mice, suggest that both an excess and a deficiency of phosphate intake may be CVD risk factors, and this study addresses the relevance of the individual components of the metabolic syndrome for CVD.

The data raise important issues for type 2 diabetes mellitus and the metabolic syndrome, which have many features that might now be attributed to low phosphate intake and the resultant low serum phosphate levels.\(^18\) These changes could be worsened by reduced renal function, which often accompanies both diabetes and aging.\(^19\) The marked increase in the incidence of diabetes, the metabolic syndrome, and the aged suggest that phosphate balance is important. The maintenance of normal phosphate balance in groups at risk for CVD adds a new dimension to the CVD prevention and treatment. Although the current study is short-term and has a small number of animals in each group, it raises a number of important issues worthy of further study in normal subjects, as well as those with lipid abnormalities, obesity, or kidney disease and the aged.

At the very least, these data suggest that future studies of CVD risk factors must include a detailed assessment of dietary intake and the source of phosphate in the diet. Others have shown that the amount of oxidants, such as advanced glycation end products, in the diet directly affects atherosclerosis in many animal models\(^20\) and CVD risk factors in normal subjects,\(^21\) subjects with the metabolic syndrome, and subjects with diabetes with\(^22\) or without chronic kidney disease.\(^18\) Importantly, the dietary content of these oxidants and phosphates can be readily controlled by dietary measures.\(^13\) In summary, the balance of substances other than classical nutrients and toxins in the diet is assuming greater significance in the current environment of mass production and processing of our food products.

**Disclosures**

None.
References


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Phosphate and CVD: It's All in What's on the Table
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